Paper No. 13

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte LINDSAY SCHWARZ, VERNON KNIGHT
and JENNIFER L. JOHNSON

Appeal No. 1999-1231
Application No. 08/709,554

ON BRIEF

Before WINTERS, WILLIAM F. SMITH and SCHEINER, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1-17.

Claims 1 and 17 are representative of the subject matter on appeal:

1. A method of increasing the cellular expression of a gene in a biological tissue in an animal to treat a pathophysiological state in said animal, comprising the steps of:

administering to said animal a vector adapted to express said gene in said tissue, wherein said gene is under control of a promoter that does not have a glucocorticoid response element and wherein expression of said gene treats a pathophysiological state in said animal; and

administering to said animal a pharmacologically effective dose of a glucocorticoid in an amount sufficient to increase the cellular expression of said gene, wherein said increase in said expression of said gene in said tissue enhances said treatment of a pathophysiological state in said animal.

17. A method of enhancing treatment of a pathophysiological state in a human by increasing cellular expression of a gene, comprising the steps of:

administering to said human a vector adapted to express said gene, wherein said gene is under control of a promoter that does not have a glucocorticoid response element and wherein administration of said gene treats a pathophysiological state in said human; and

administering to said human a pharmacologically effective dose of a glucocorticoid in an amount sufficient to increase the cellular expression of said gene, wherein said increase in said expression of said gene in said tissue enhances said treatment of a pathophysiological state in said human.

The references relied on by the examiner are:

Hirt et al. (Hirt), "Inducible Protein Expression Using a Glucocorticoid-Sensitive Vector," Methods in Cell Biology, Vol. 43, pp.247-262 (1994)

Günzburg et al. (Günzburg), "Virus Vector Design in Gene Therapy," Molecular Medicine Today, Vol. 1, No. 9, pp. 410-417 (1995)

Marshall, "Less Hype, More Biology Needed for Gene Therapy," Science, Vol. 270, p. 1751 (1995)

Ledley, "Nonviral gene Therapy: The Promise of Genes as Pharmaceutical Products," Human Gene Therapy, Vol. 6, pp. 1129-1144 (September 1995)

Coghlan, "Gene Dream Fades Away," New Scientist, Vol. 148, pp. 14-15 (November, 1995)

Claims 1-17 stand rejected under the first paragraph of 35 U.S.C. § 112, as based on a non-enabling disclosure. In addition, claims 1-17 stand rejected under the second paragraph of 35 U.S.C. § 112.

We reverse the examiner's rejections.

BACKGROUND

According to the specification, the present invention "has direct relevance to the use of gene therapy in vivo" and is based on "two findings which have a substantial effect on transfection in cell culture and which have parallels in vivo." First, according to appellants, is the finding that "IL-1β and . . . lipopolysaccharide (LPS) suppress transfection/expression of [reporter genes] transfected into [cells] . . . by cationic lipid;"

second, that "anti-inflammatory topical glucocorticoids . . . reverse the inhibitory effects of IL-1β and lipopolysaccharide and even enhance expression of reporter genes above and beyond expression seen in untreated transfected cells." Specification, pages 3-4. Based, at least in part, on studies described in Examples 10 through 16 of the specification, appellants conclude that the enhanced gene expression observed with glucocorticoids "is specific to glucocorticoids, as opposed to other types of steroids, but not to a particular glucocorticoid;" it "is independent of promoter, reporter gene and cationic lipid used;" and it "does not involve increased plasmid-lipid uptake, but rather an intracellular mechanism which does not involve new protein synthesis." Id., page 4. Instead, appellants suggest that their results demonstrate "that either transcription [is] increased or [ ] mRNA [is] stabilized in the cytoplasm by glucocorticoids." Id., page 30.

DISCUSSION

Enablement

According to the examiner, "[t]he intended use of the invention is for increasing cellular expression of a gene . . . after delivery of said gene . . . into a biological tissue of a human . . . so as to have a therapeutically enhancing effect," but "[t]he specification does not reasonably provide enablement for methods of increasing cellular expression of a gene in vivo [or] for treatment methods." Examiner's Answer, page 5. Appellants acknowledge that the claimed invention is indeed "directed [to] a method of enhancing gene expression concomitant with gene therapy" (Brief, page 8), but argue that "the unpredictability of gene therapy . . . does not preclude [the] specification from enabling the claimed invention" (Id.), inasmuch as the invention "is directed [to] a method of improving the current limitations of gene therapy" (Id., page 6).

In reviewing the examiner's analysis in support of the rejection under the first

paragraph of § 112, it appears that his conclusion is based on two principle misgivings. The first concerns the field of gene therapy generally, while the second is more specific to the claimed invention as it concerns the role of "glucocorticoids in combination with gene transfer techniques" (Examiner's Answer, page 10).

The examiner cites several references in support of his assertion that, "[a]t the time of filing, . . . gene therapy [was] in its infancy and [ ] highly unpredictable" and "remains at a very early stage of development." Examiner's Answer, page 8. If we understand the examiner's position, it is that the field of gene therapy, generally, will not be enabled so long as it remains "experimental and unpredictable and, . . . unproven for general treatment." Id., page 13. However, this position does not reflect the applicable legal standard.

In In re Brana, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995), the court cautioned against confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption," citing Scott v. Finney, 34 F3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). The rejection before the court for review in Brana was for lack of enablement under the first paragraph of 35 U.S.C. § 112 (although the court discussed the issues raised in the appeal in the context of both enablement and the utility requirement of 35 U.S.C. § 101):

> On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. [ ] Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. [ ]

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. [ ] Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana, 51 F3d at 1568, 34 USPQ2d at 1442-43 (citations omitted). While the claims involved in Brana were directed to chemical compounds taught to be useful in treating cancer, we believe these principles can be applied to the present claims directed to methods of gene therapy, especially in light of the examiner's apparent holding that gene therapy in general is non-enabled.

The references relied on by the examiner support his position that the future course of gene therapy was uncertain at the time the present application was filed. Nevertheless, these same references provide evidence that the field had reached that stage of "[u]sefulness in patent law" described in Brana. For example, in a 1995 article discussing viral gene transfer systems, Günzburg cited "over 140 human gene therapy trials on the way to the clinic, with yet more planned." Page 417. Similarly, in a 1995 review article, Ledley listed "[m]ore than a dozen clinical trials [ ] currently underway using nonviral systems for disease indications including cystic fibrosis and cancer." Page 1129.

Our review of the examiner's evidence in light of the standard for enablement and/or utility articulated in Brana leads us to conclude that the evidence does not support the broad proposition that gene therapy is nonenabled.

Turning to that aspect of the examiner's rejection that focuses on the role of glucocorticoids in gene transfer techniques, the examiner cites Hirt as evidence that glucocorticoids exert their biological effects by binding to glucocorticoid response elements (GREs) in the promoter regions of glucocorticoid-regulated genes, that their effects on the activity of glucocorticoid-inducible promoters are extensive and varied, and "that there are 'some problems and limitations inherent in inducible expression systems, especially in glucocorticoid-inducible expression vectors'." Examiner's Answer, pages 10-11.

Inasmuch as the examples in the specification purport to demonstrate that glucocorticoids have an effect on gene expression that is independent of the promoter or gene used, and the claimed method expressly requires a vector containing a gene under the control of a promoter that does not have a GRE, the relevance of Hirt is not immediately apparent. Nevertheless, the examiner insists that "[t]he promoter needs to have a glucocorticoid response element for glucocorticoid to have an effect on the promoter" (Examiner's Answer, page 5), and that the CMV and SV40 promoters used in the examples may lack "the more common glucocorticoid response element[s]," but that does not prove that they "have no GRE at all" (Id., page 8). The examiner concludes that "[f]or a glucocorticoid to have an effect, it is therefore apparent that there is a GRE but for which the instant claims require there be no GRE" (Id., page 11).

We remind the examiner that

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). Moreover,

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

Id. at 224, 169 USPQ at 370.

In our view, the evidence or reasoning advanced by the examiner amounts to unsupported assertions inadequate to outweigh the evidence of appellants' "presumptively accurate disclosure." On this record, we hold that the examiner has failed to establish that the claimed subject matter is non-enabled. Accordingly, the rejection of claims 1 through 17 under the first paragraph of 35 U.S.C. § 112 is reversed.

Indefiniteness

According to the examiner, "it is not apparent as to what is exactly meant by the phrase 'administering to said animal a vector adapted to express [a] gene'" in claims 1 and 17 because "there is no indicated effect upon the animal (i.e., phenotypic change or a therapeutic effect) from the expression of the gene." Examiner's Answer, page 14. In our view, the phrase is not indefinite when read in conjunction with the clause that recites that "expression of the gene treats a pathophysiological state." While the claims are broad, "[b]readth is not indefiniteness." In re Gardner, 427 F.2d 786, 788, 166

USPQ 138, 140 (CCPA 1970).

In addition, in claim 9, the examiner finds the phrases “prior to” and “after” administration of the vector to be indefinite because “the phrases are not defined in the specification.” Nevertheless, we hold that the claim is not indefinite when read in light of the claim it depends from, and the specification.

The rejection of claim 1 through 17 as indefinite under the second paragraph of 35 U.S.C. § 112 is reversed as well.

REVERSED

Sherman D. Winters Administrative Patent Judge	)
	) BOARD OF PATENT
William F. Smith Administrative Patent Judge	) APPEALS AND)
	))INTERFERENCES
Toni R. Scheiner Administrative Patent Judge	)

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